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Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN®, botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia ☆

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ABSTRACT

Objective: IncobotulinumtoxinA differs from available formulations in that it does not have accessory proteins. IncobotulinumtoxinA has previously shown non-inferiority to onabotulinumtoxinA for the treatment of CD with a 1:1 dosing regimen. The objective of this study was to compare the safety and efficacy of incobotulinumtoxinA (120 U, 240 U; Merz Pharmaceuticals) to placebo in subjects with cervical dystonia (CD).
Methods: This was a prospective, double-blind, randomized, placebo-controlled, multicenter clinical trial in botulinum toxin-treated or toxin-naïve CD patients. The primary outcome measure was change from baseline to Week 4 on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total score. Adverse events (AEs) also were evaluated.
Results: Participants (N = 233) were mostly women (66%), a mean of 52.8 years old, who had CD for a mean of 51.9 months. Of those, 39% were toxin-naïve. IncobotulinumtoxinA significantly improved TWSTRS-Total scores from baseline to Week 4 compared to placebo (placebo = −2.2; 120 U = −9.9, and 240 U = −10.9; 240 U vs. placebo $p<0.001$ and 120 U vs. placebo $p<0.001$). This effect persisted through to the end of the study. The most frequently reported AEs in the incobotulinumtoxinA groups were dysphagia, neck pain, and muscular weakness which were generally mild. Interpretation: IncobotulinumtoxinA (at doses of 120 U or 240 U) is a safe and effective treatment for CD in previously-treated as well as toxin-naïve subjects.

1. Introduction

Cervical dystonia (CD) is a focal dystonia that causes abnormal postures of the head, neck and shoulders. Class A evidence has established botulinum toxin treatment as an effective means to control the symptoms of CD [1]. IncobotulinumtoxinA (marketed as XEOMIN® in the US, Canada and Europe, Merz Pharmaceuticals, GmbH, Frankfurt) is a botulinum toxin serotype A that differs from other available botulinum toxin formulations in that the botulinum toxin complex is purified from the culture supernatant and then the active ingredient is separated from the proteins (hemagglutinins and non-hemagglutinins) through a series of steps yielding the active neurotoxin with molecular weight of 150 kDa, without accessory proteins [2]. Whether the absence of accessory proteins confers unique qualities in the therapeutic use of botulinum toxin has not been established. The incobotulinumtoxinA formulation contains only the active portion of the clostridial protein per vial [3,4] and has long-term stability at room temperature (up to 4 years) [5]. Non-inferiority studies in patients with blepharospasm and CD have shown similar effects of onabotulinumtoxinA and incobotulinumtoxinA [6,7].

The specific aim of this study was to evaluate symptom improvement and tolerability associated with a single injection of incobotulinumtoxinA compared to placebo.

2. Methods

This was a prospective, multicenter, double-blind, randomized, placebo-controlled study conducted at 37 sites in the US. The respective Institutional Review Boards approved the study protocol and informed consent process. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and is consistent with Good Clinical Practice and the applicable regulatory requirements. Prior to screening, all subjects provided written informed consent. The study was registered with clinicaltrials.gov (www.clinicaltrials.gov) [Identification number: NCT00407030].

2.1. Subjects

The study was conducted between July, 2006 and March, 2008. Eligible subjects were men or women between the ages of 18 and

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75 years with a history of primary CD with predominantly rotational form, a baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total score ≥20, and TWSTRS subscale scores as follows: Severity ≥10, Disability ≥3, and Pain ≥1. Both previously treated patients and those never exposed to botulinum toxin were included. Pre-treated subjects were required to be stable responders, receiving no more than 300 U botulinum toxin type A or 12,000 U botulinum toxin type B. The last injection for those previously treated had to be at least 10 weeks prior to entry. Subjects were excluded if they had any of the following: predominant anterocollis or retrocollis (TWSTRS score for either of these items >2); previous surgery for CD; significant neuromuscular disease; severe dysphagia; blood coagulation disorders or anticoagulation therapy; pregnancy or lactation; treatment with botulinum toxin for any indication other than CD within 4 months prior to baseline and during the trial; cervical contractures or significant cervical spine disease that impaired range of motion; uncontrolled medical disorders. Concomitant treatment with phenol or alcohol injections or local anesthetics in the affected area anticipated was not permitted. Treatment with intrathecal baclofen was not allowed within two weeks prior to screening or during the trial. Parenterally administered drugs that interfere with neuromuscular transmission (e.g., tubocurarines, volatile anesthetics and barbiturates), aminoglycosides or aminoquinolones were not allowed during the trial. Subjects taking medications for focal dystonia (e.g. anticholinergics and benzodiazepines) were required to be on a stable dose for at least 3 months prior to and throughout the trial.

2.2. Randomization

Subjects were randomized to one of three arms: placebo, incobotulinumtoxinA 120 U, or incobotulinumtoxinA 240 U using a balanced ratio of 1:1:1. Randomization was performed using RANCODE version 3.6 (IDV, Gauting). Block-wise randomization by previous treatment with botulinum toxin ensured a balanced treatment assignment for each center for pretreated and treatment-naïve patients. Subjects, investigators, medical staff, biostatisticians responsible for data analysis, data managers and monitors were blind to subjects' treatment group.

The trial was monitored by an independent Data Safety Monitoring Board [DSMB]. The primary purpose of the DSMB was to monitor the overall safety of subjects and to make recommendations regarding subject withdrawals, dose modifications and/or study suspension. The DSMB biostatistician was independent from all staff involved in the evaluation of study data and provided the DSMB with adverse event (AE) listings by treatment group.

2.3. Study drug and injection technique

Subjects were treated only once, at the baseline visit. They received either 120 U or 240 U of incobotulinumtoxinA, or placebo, depending on the group to which they had been randomized. The total volume administered for all three groups was 4.8 mL for the unique injection. The number of injection sites per muscle, the volume injected into each muscle, and the use of electromyographic (EMG) guidance were determined at the discretion of the investigator.

2.4. Study visits

Visit 1 occurred 7 days (±3 days) prior to the baseline visit to obtain informed consent and to evaluate inclusion and exclusion criteria. At this visit, subjects underwent laboratory testing, electrocardiogram, and assessment of the TWSTRS (see Outcome measures). In addition, vital signs were assessed and a structured dysphagia scale was completed.

At the baseline visit, eligibility criteria and efficacy scales were evaluated again and subjects were randomized to one of three study arms (placebo, incobotulinumtoxinA 120 U, or 240 U). Subjects were injected with the study drug appropriate to their randomized grouping.

One week after the baseline visit, subjects were contacted by telephone to inquire about any changes in concomitant medication or diseases, and adverse events, including dysphagia. Four weeks following the baseline visit, subjects returned to the office for evaluation on the primary outcome measure (TWSTRS-Total score). Adverse events and secondary outcome measures were also assessed. Subjects were evaluated again at 8 weeks post-injection, and then maintained contact with the study site (at least every 2 weeks) either in person or by telephone, until the reinjection was indicated, or up to 20 weeks following baseline injection. Reinjection was indicated based on the clinical need and/or a return to TWSTRS-Total score ≥20. Reinjection was permitted as early as 8 weeks following the initial injection. Subjects not requiring reinjection were followed for a maximum of 20 weeks and the final visit occurred at that time.

2.5. Outcome measures

2.5.1. Efficacy

The primary efficacy outcome measure was change in TWSTRS-Total score from baseline to Week 4. The TWSTRS is a standard rating scale (range, 0–85) for measurement of the severity of CD [8]. The total score is the sum of 3 subscale scores: Severity (maximal score 35), Disability (maximal score 30), and Pain (maximal score 20). The same investigator performed all assessments for a given subject. In order to reduce inter-rater variability across sites, all investigators were required to undergo standardized video-based training that included the scoring of test cases within a prespecified range.

Secondary efficacy measures included change from baseline to Week 4, Week 8 and final visit for the TWSTRS subscales of Motor Severity, Disability, and Pain, as well as change from baseline to Week 8 and final visit for TWSTRS-Total score. Additional secondary and tertiary efficacy measures included the Patient Evaluation of Global Response (PEGR) and the Investigator Global Assessment of Efficacy (IGAE). The PEGR is a patient-administered scale, ranging from very marked worsening (−4) to complete resolution of CD signs and symptoms (+4), and was obtained at the final visit of the study. The IGAE is completed by the investigator and is a 4-point Likert scale with outcome assessed as very good, good, moderate, or poor for efficacy. The IGAE was performed at the final visit.

2.5.2. Safety

Adverse events were evaluated during each visit and each telephone contact. Subjects were asked to report all AEs to the investigator. Dysphagia was determined at baseline and subsequent study visits using a structured interview that included 5 items ranging from no swallowing difficulties to swallowing not possible and resulting in weight loss. Standard clinical chemistry and hematology tests were conducted at baseline and at the final visit. The Global Assessment of Tolerability (IGAT) was performed by the investigator at the final visit and is a 4-point Likert scale with outcome assessed as very good, good, moderate, or poor for efficacy.

2.6. Statistical methodology

2.6.1. Sample size determination

The sample size was based upon a 2-sided *t*-test at 5% level of a treatment effect between the 240 U group and placebo. A study with 49 completed subjects per group had 90% power to detect a treatment difference, assuming a mean change from baseline in TWSTRS-Total score of 4 points for placebo and of 10 points for 240 U group, with a common standard deviation (SD) of 9 points [9–11]. The sample size was increased to 59 subjects per group to increase the database size for safety assessments and to increase the power for demonstrating a difference in the primary efficacy assessment between the 120 U

group and placebo. Assuming a 20% dropout rate, a target of 74 subjects per treatment group was required, with a total sample size of 222 subjects. This study was not powered to detect a difference between the two dose groups of incobotulinumtoxinA in the primary efficacy assessment.

2.6.2. Statistical analyses

All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). Efficacy was analyzed using the intent-to-treat (ITT) population which included all randomized subjects. Data on the treated-per-protocol (TPP) population, including all ITT subjects without major protocol violations, were used for supportive analyses. The primary efficacy parameter was the change from Baseline (Visit 2, Day 0) to Visit 3 (Week 4) in the TWSTRS-Total score. The confirmatory analysis of the primary efficacy parameter was based on the comparison of least square (LS) means from an analysis of covariance (ANCOVA) model at Week 4 between treatment groups with change from baseline of the TWSTRS-Total score as dependent variable and treatment, baseline TWSTRS-Total score, gender, age, pre-treatment of cervical dystonia, and pooled center as independent variables using the ITT population. Comparisons between treatment groups were performed by using a fixed-sequence test procedure (step downward) in the ITT Population. Due to the fixed-sequence test procedure, no type-I error adjustment was necessary and all tests of the fixed-sequence test procedure were performed two-sided with a type-I error of $\alpha = 0.05$. In case of missing data for the change from baseline of the TWSTRS-Total score, a conservative replacement with a change score of "0" (no change) was applied. Type III Sum of Squares was used for testing procedures. As secondary analyses, the same analysis performed for Week 4 was also performed for the TWSTRS-Total score obtained at Week 8 and the final visit as well as for the TWSTRS-Severity score, TWSTRS-Disability score, and the TWSTRS-Pain score for Week 4, Week 8, and the final visit. All 3 treatment comparisons were tested in the ANCOVA models as described for the primary efficacy endpoint above using the baseline subscale score instead of the baseline total score as covariate for the tests performed on the TWSTRS subscales. The evaluations were conducted for the ITT and supportive for the TPP population. Furthermore, descriptive summary statistics were calculated.

The PEGR was analyzed at the final visit using an ANCOVA procedure in the ITT population. Model building was performed analogously to the primary efficacy parameter. Missing data of this endpoint were set to a zero effect (value = 0). In addition, descriptive summary statistics and frequency tables were calculated.

The IGAE summary statistics as well as frequency tables were computed. For treatment comparisons, pair-wise, descriptive Mann–Whitney-Tests were performed.

All subjects who received the study medication were included in the descriptive safety analysis. AEs were encoded using MedDRA version 9.1.

3. Results

3.1. Subjects

Of the 301 subjects screened, 68 did not meet inclusion or exclusion criteria and were excluded from the study. The most frequent reasons for not meeting inclusion or exclusion criteria were: TWSTRS-Severity score <10; TWSTRS-Total score <20; TWSTRS-Disability score <3; absence of CD symptoms; and absence of source documentation of the last two consecutive injection sessions with botulinum toxin, or unstable therapeutic response directly prior to trial entry. A total of 233 subjects were randomized as the ITT population, with 74 subjects receiving placebo, 78 receiving 120 U, and 81 receiving 240 U (Fig. 1). At baseline, there were no significant differences in demographic features among the three groups (Table 1). Seventy-nine men and 154 women participated, with a mean age of 52.8 years (SD = 11.5) and mean CD duration of 51.9 months (SD = 68.2). Of these, 143 were previously treated with botulinum toxin, and 90 were treatment-naïve. At baseline, the TWSTRS-Total score did not differ among the 3 groups.

3.2. Efficacy

3.2.1. Primary outcome

Improvement in CD as reflected by a decrease in TWSTRS-Total scores at Week 4 post-injection was significant in both the 120 U and 240 U groups compared to placebo (Table 2).

3.2.2. Secondary outcomes

The TWSTRS subscales for motor severity, disability and pain were improved from baseline in both active groups vs. placebo at Weeks 4, 8 and final visits. The TWSTRS-Total score was improved from baseline in the active groups vs. placebo at Week 8 and at the final visit (Table 2).

The PEGR showed significant improvement in the 120 U group (mean change 1.3, SD = 1.77) and the 240 U group (mean change 1.3, SD = 1.84) compared to placebo (mean change −0.2, SD = 1.34); ($p < 0.001$ for both 120 U vs. placebo and 240 U vs. placebo). The most frequent category chosen in the 120 U and the 240 U dose groups was "marked improvement", while the most frequently used category in the placebo group was "unchanged" (Table 3). No difference was observed between the 120 U and the 240 U groups ($p = 0.930$).

The mean score (SD) on the IGAE was 2.5 (SD = 1.21) in the 120 U group and 2.3 (SD = 1.23) points in the 240 U group, which corresponds to a good overall response. In the placebo group, the mean score was 3.6 (SD = 0.85), which corresponds to a poor to moderate response. The investigator classified the therapeutic efficacy of the 120 U dose and the 240 U dose as very good (26.9% and 35.8%, respectively) or good (24.4% and 21%, respectively). In the placebo group, the investigator classified the global assessment of efficacy as "poor" in 70% of subjects.

3.3. Safety

Adverse events are summarized in Table 4. The most frequently reported AEs that were considered to be related to treatment by the investigator included dysphagia, neck pain and muscular weakness. Almost all treatment-related AEs were of mild or moderate severity. Severe treatment-related AEs were reported in 4 (5.1%) subjects in the 120 U group (musculoskelatal pain (n = 1); neck pain (n = 1); headache (n = 1) and dizziness (n = 1)) and 4 (4.9%) subjects in the 240 U group (muscular weakness (n = 3); musculoskeletal stiffness (n = 1); injection site pain (n = 1) and neck pain (n = 1)). One of the 4 subjects in the 120 U group and all 4 subjects in the 240 U group were treatment-naive. There were 4 serious adverse events reported in 4 subjects, all in the 240 U group; however, all were considered unrelated to study medication by the investigator (n = 1 severe appendicitis, n = 1 severe staphylococcal infection, n = 1 moderate asthma (in a subject with a history of asthma) and n = 1 severe COPD (in a subject with a history of asthma and COPD)).

At baseline, the majority of subjects (63 [80.8%] in the 120 U group, 70 [86.4%] in the 240 U group, and 66 [89.2%] in the placebo group) reported no swallowing difficulties (Fig. 2). After injection of study medication, the majority of subjects in all groups continued to report no dysphagia. There was no increase in the percentage of subjects with moderate difficulties in swallowing in any treatment group, and no subjects had severe difficulties in swallowing at any point post-injection. There were no marked changes from screening to the final visit for any laboratory parameters (hematology or biochemistry) and no marked differences between treatment groups. Throughout the study, the means of all vital sign parameters as well as body weight

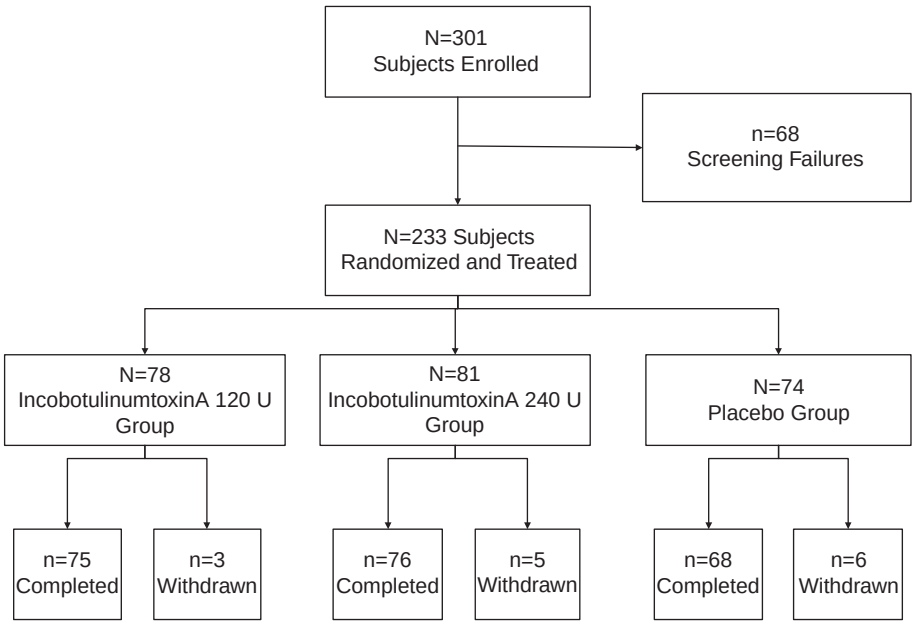

Fig. 1. Subject disposition. See attached.eps graphic file. Three subjects discontinued the study prematurely due to AEs: 1 subject in the 240 U group experienced musculoskeletal pain, neck pain and muscle weakness, another subject in the 240 U group experienced muscle weakness, 1 subject in the 120 U group experienced nausea and dizziness. Three subjects in the placebo group were withdrawn due to insufficient efficacy. Three subjects (one in each group) withdrew consent, 3 subjects (one in each group) were lost to follow up, 1 subject in the placebo group moved out of the country (occurrence of withdrawal criteria) and 1 subject in the 240 U group withdrew for family reasons.

remained essentially unchanged at similar levels in all treatment groups.

3.3.1. Investigator Global Assessment of Tolerability (IGAT)

There were no relevant differences between groups with regard to global assessment of tolerability. The investigator classified the tolerability of study medication as very good (1) or good (2) in 88.5% of 120 U subjects, 91.4% of 240 U subjects, and 85.1% of placebo subjects. The mean (SD) tolerability scores were 1.5 (SD = 0.72), 1.4 (SD = 0.78), and 1.5 (SD = 0.79) for the 120 U, 240 U, and placebo groups, respectively. The differences between groups were not statistically significant (Mann–Whitney test: 120 U vs. Placebo, $p = 0.784$; 240 U vs. Placebo, $p = 0.807$; 240 U vs. 120 U, $p = 0.578$).

4. Discussion

In this randomized, double-blind, placebo-controlled study, both doses of incobotulinumtoxinA (120 U and 240 U) were significantly more efficacious than placebo in reducing the symptoms of CD. Four weeks after injection, improvement in symptoms was greater in both active treatment groups compared to placebo on TWSTRS Total and subscale scores. There was continued improvement at Week 8 and at

Table 1
Baseline characteristics (intent-to-treat population).

	Placebo	IncobotulinumtoxinA 120 U	IncobotulinumtoxinA 240 U
	n = 74	n = 78	n = 81
Mean age, yrs (SD)	52.4 (10.8)	52.8 (11.5)	53.2 (12.2)
Female subjects, no. (%)	49 (66.2)	51 (65.4)	54 (66.7)
Estimated mean duration of CD (months), mean (SD)	129.7 (107.7)	111.0 (100.5)	116.7 (107.4)
Botulinum toxin naïve, no. (%)	28 (38)	31 (40)	31 (38)
TWSTRS-Total, mean (SD)	41.8 (7.9)	42.6 (9.7)	42.1 (9.3)
TWSTRS-Severity, mean (SD)	18.9 (3.5)	18.0 (4.4)	18.6 (4.1)
TWSTRS-Disability, mean (SD)	11.8 (3.9)	13.1 (4.4)	12.5 (4.6)
TWSTRS-Pain, mean (SD)	11.1 (3.8)	11.5 (4.0)	11.0 (4.0)
Completed subjects, no. (%)	68 (91.9)	75 (96.2)	76 (93.8)
Withdrawn subjects, no (%)	6 (8.1)	3 (3.8)	5 (6.2)
Reasons for premature termination			
Withdrawal criteria occurred	1 (1.4)	0 (0.0)	0 (0.0)
Insufficient efficacy	3 (4.1)	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	1 (1.3)	2 (2.5)
Consent withdrawn	1 (1.4)	1 (1.3)	1 (1.2)
Lost to follow-up	1 (1.4)	1 (1.3)	1 (1.2)
Other	0 (0.0)	0 (0.0)	1 (1.2)
Botulinum toxin type and mean and median doses of last injection prior to study entry n (%); mean (median)			
OnabotulinumtoxinA, n (%)	40 (87.0);	41 (87.2);	43 (86.0);
	232.5 (250)	219.4 (225)	222.9 (220)
AbobotulinumtoxinA, n (%); U	0 (0);	2 (4.3);	3 (6.0);
	0 (0)	500 (500)	550 (450)
RimabotulinumtoxinB, n (%); U	6 (13.0);	4 (8.5);	4 (8.0);
	10,200 (10,000)	12,000 (12,000)	10,875 (12,000)

No. = number; SD = standard deviation; % = percentage; yrs = years.

Table 2
Changes in TWSTRS-Total and TWSTRS subscales at 4 and 8 weeks and at the Final Visit (intent to treat population; missing values replaced by subject's baseline value).

	Placebo	IncobotulinumtoxinA 120 U	Adjusted Mean difference[a] 120 U-placebo (95% CI)	IncobotulinumtoxinA 240 U	Adjusted Mean difference[a] 240 U-placebo (95% CI)
	n = 74	n = 78		n = 81	
	Mean Δ (SD)	Mean Δ (SD)		Mean Δ (SD)	
TWSTRS: Week 4					
Total	−2.2 (7.3)	−9.9 (10.4)	−7.5 (−10.4; −4.6) p<0.001	−10.9 (11.7)	−9.0 (−12.0; −5.9) p<0.001
Severity	−1.9 (4.0)	−3.9 (4.3)	−2.1 (−3.4; −0.7) p = 0.003	−5.5 (6.0)	−3.9 (−5.5; −2.3) p<0.001
Disability	0.0 (3.4)	−3.3 (4.7)	−2.9 (−4.2; −1.6) p<0.001	−3.0 (4.4)	−2.8 (−4.1; −1.6) p<0.001
Pain	−0.3 (3.0)	−2.7 (4.6)	−2.2 (−3.5; −1.0) p<0.001	−2.4 (4.4)	−2.2 (−3.4; −1.1) p<0.001
TWSTRS: Week 8					
Total	0.4 (7.2)	−6.9 (11.2)	−7.1 (−10.1; −4.2) p<0.001	−8.2 (10.5)	−8.6 (−11.5; −5.8) p<0.001
Severity	−0.9 (3.6)	−3.1 (4.4)	−2.2 (−3.5; −1.0) p = 0.001	−3.5 (5.4)	−2.7 (−4.2, −1.3) p<0.001
Disability	0.8 (3.3)	−2.1 (4.9)	−2.4 (−3.7; −1.1) p<0.001	−2.4 (4.0)	−3.0 (−4.1; −1.8) p<0.001
Pain	0.6 (2.8)	−1.8 (4.1)	−2.3 (−3.4, −1.1) p<0.001	−2.3 (4.3)	−2.9 (−4.1, −1.8) p<0.001
TWSTRS: Final Visit					
Total	1.7 (6.2)	−3.6 (8.1)	−5.2 (−7.4; −3.0) p<0.001	−4.6 (7.5)	−6.4 (−8.6; −4.2) p<0.001
Severity	−0.2 (3.1)	−1.1 (3.2)	−1.2 (−2.1, −0.2) p = 0.02	−1.9 (3.8)	−1.9 (−3.0; −0.8) p = 0.001
Disability	1.0 (3.3)	−1.4 (3.8)	−2.0 (−3.1; −0.9) p = 0.001	−1.3 (3.1)	−2.2 (−3.2; −1.2) p<0.001
Pain	0.9 (2.6)	−1.1 (4.0)	−1.9 (−2.9; −0.8) p<0.001	−1.3 (3.4)	−2.3 (−3.3; −1.4) p<0.001

CI = confidence interval; SD = standard deviation.
[a] Adjusted mean differences based on Least-Square means and the full statistical model.

the final visit in comparison to baseline. Similarly, the PEGR and IGAE also demonstrated improvements at each post-injection visit. The results from this study are consistent with other studies of botulinum toxins for treatment of CD [1].

The lower dose (120 U) of incobotulinumtoxinA used in this study was selected on the basis of the doses of incobotulinumtoxinA utilized in a non-inferiority study published earlier (median dose 122.5 U) [7]. The higher dose (240 U) was chosen based on the safety studies performed with onabotulinumtoxinA [12].

The present study was not powered to detect a difference between the two active treatment groups (incobotulinumtoxinA 120 U and 240 U). However, there was a slightly larger mean change in the TWSTRS-Total in the 240 U group than in the 120 U group and the higher dosage group showed a significantly greater improvement in the TWSTRS-Severity subscale.

There were no new or unexpected safety findings with incobotulinumtoxinA. The most frequently reported AEs included dysphagia, neck pain and muscular weakness, all of which were more frequent with the active treatment arms than with the placebo treatment. These AEs are consistent with the previously reported studies of incobotulinumtoxinA [7] and are similar to those reported in trials of abobotululinumtoxinA [11,13] and onabotulinumtoxinA [12].

Table 3
Patient evaluation of global response at final visit (ITT population).

	Placebo	IncobotulinumtoxinA 120 U	IncobotulinumtoxinA 240 U
	N = 74	N = 78	N = 81
	n (%)	n (%)	n (%)
Complete abolishment of all signs and symptoms	0	7 (9.0)	2 (2.5)
Marked improvement	3 (4.1)	19 (24.4)	29 (35.8)
Moderate improvement	5 (6.8)	12 (15.4)	12 (14.8)
Slight improvement	7 (9.5)	12 (15.4)	11 (13.6)
Unchanged	33 (44.6)	15 (19.2)	17 (21.0)
Slight worsening	8 (10.8)	5 (6.4)	2 (2.5)
Moderate worsening	11 (14.9)	4 (5.1)	2 (2.5)
Marked worsening	3 (4.1)	0	4 (4.9)
Very marked worsening	0	1 (1.3)	1 (1.2)
Missing	4 (5.4)	3 (3.8)	1 (1.2)

Table 4
Treatment-emergent adverse events (safety population).

	Placebo	IncobotulinumtoxinA 120 U	IncobotulinumtoxinA 240 U
	n = 74	n = 78	n = 81
	n (%)	n (%)	n (%)
TEAEs affecting >5% of subjects in any treatment group			
Subjects with ≥1 TEAE	34 (45.9)	43 (55.1)	46 (56.8)
Dysphagia	2 (2.7)	9 (11.5)	15 (18.5)
Neck pain	3 (4.1)	4 (5.1)	12 (14.8)
Muscular weakness	1 (1.4)	5 (6.4)	9 (11.1)
Musculoskeletal pain	1 (1.4)	6 (7.7)	3 (3.7)
Injection site pain	4 (5.4)	7 (9.0)	3 (3.7)
Nasopharyngitis	5 (6.8)	3 (3.8)	0 (0)
Related[a] TEAEs >5% of subjects in any treatment group			
Subjects with ≥1 related TEAE	11 (14.9)	28 (35.9)	29 (35.8)
Dysphagia	2 (2.7)	8 (10.3)	13 (16.0)
Neck pain	1 (1.4)	4 (5.1)	10 (12.3)
Muscular weakness	1 (1.4)	5 (6.4)	8 (9.9)
Musculoskeletal pain	0	5 (6.4)	3 (3.7)
Injection site pain	4 (5.4)	7 (9.0)	3 (3.7)

TEAE = treatment emergent adverse event.
[a] Relationship assessed by investigator.

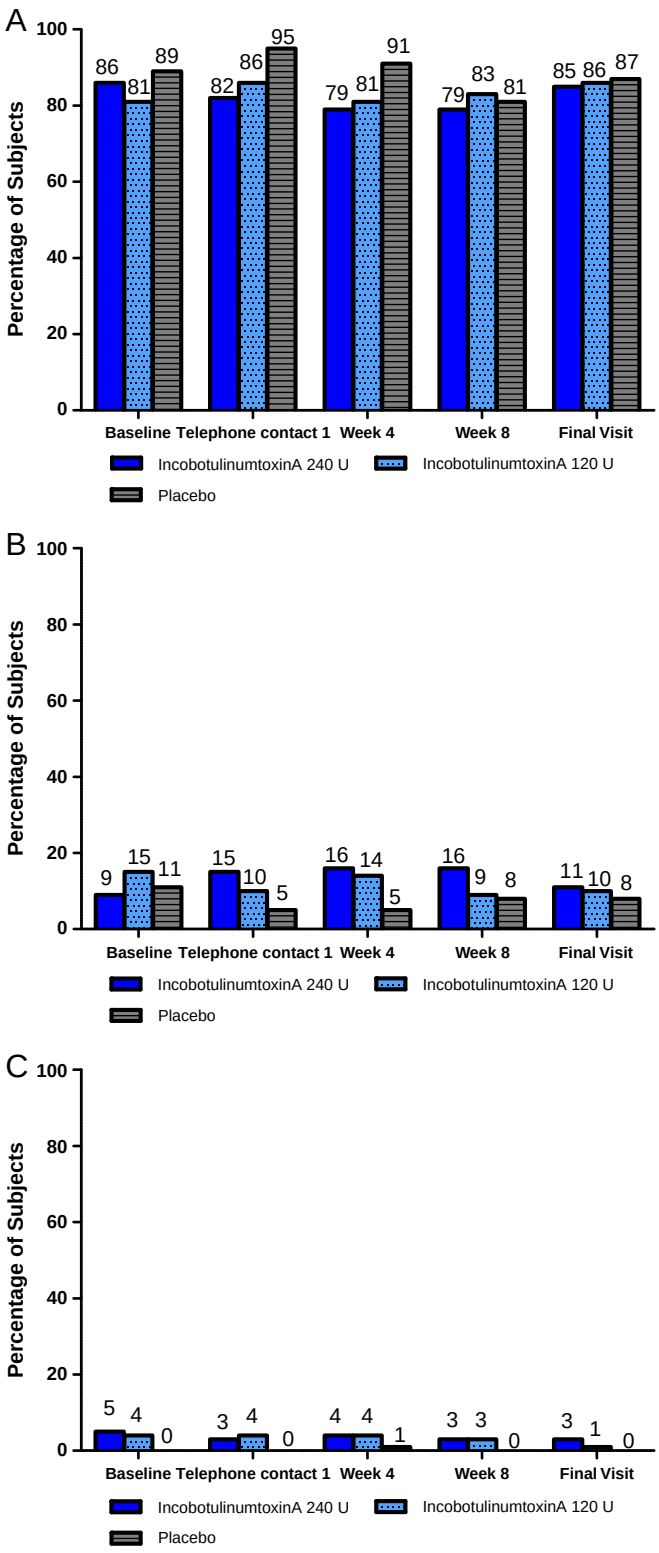

Fig. 2. Dysphagia Score by Visit. A: Dysphagia Score by Visit — Score 0 (Absent). B: Dysphagia Score by Visit — Score 1 (Mild). C: Dysphagia Score by Visit — Score 2 (Moderate). Dysphagia Scores: 0 = Absent, no swallowing difficulties; 1 = Mild swallowing difficulties; 2 = Moderate, when swallowing solid meals (e.g., meat); 3 = Severe, with swallowing difficulties and requiring a diet change; 4 = Swallowing not possible, resulting in weight loss. After injection of study medication, the majority of subjects in all groups had no change in dysphagia score. There was no increase in the percentages of subjects with moderate difficulties in swallowing in any treatment group and no subjects had severe difficulties in swallowing at any point post-injection.

Dysphagia and muscular weakness were the most frequently reported treatment-emergent AEs of special interest, showing a dose-dependent increase in incobotulinumtoxinA treated subjects. Importantly, there was no increase in the percentages of subjects with moderate difficulties in swallowing in any treatment group and no subjects had severe difficulties in swallowing at any point post-injection as measured by the Dysphagia Scale. These findings are similar to a prior study of incobotulinumtoxinA which used the Dysphagia Scale as an outcome measure [14], and to other studies that systematically evaluated dysphagia following botulinum toxin treatment [15].

The strength of this study is the inclusion of two treatment arms compared to placebo, which demonstrates that either dose is both safe and effective. However, the fixed dosages are also one of the limitations of the study in that no dosing flexibility was permitted in order to optimize therapy. A second limitation of this placebo-controlled study was the assessment of safety and efficacy following a single injection series. Clinical change using botulinum toxins is best assessed when subjects receive multiple injection series at flexible dosing, allowing for adjustments of treatment for each individual patient.

The unique feature of incobotulinumtoxinA is that it is the only botulinum toxin product that contains the 150 kD neurotoxin without accessory proteins. Accessory proteins consist of hemagglutinin and non-hemoagglutinin components. The primary role of these proteins is to prevent proteolytic cleavage of the toxin in the gut in food-borne botulism [16,17]. Following entry into the lymphatic system and then the blood stream, the neurotoxin is rapidly dissociated from the accessory proteins. Whether accessory proteins have any important effects following intramuscular injection of botulinum toxin is not known. Although some have suggested less immunogenicity of the neurotoxin without accessory proteins, this has not been established.

Overall, this study demonstrates that incobotulinumtoxinA, at either 120 U or 240 U, was a safe and effective treatment for CD for a study duration of up to 20 weeks.

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Appendix 2. Author conflict of interest disclosures

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References

[1] Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008;70(19):1699–706.

[2] Merz Pharmaceuticals, LLC. XEOMIN® (incobotulinumtoxinA) for injection US Prescribing Information; 2010.

[3] Frevert J. Xeomin is free from complexing proteins. Toxicon 2009;54(5):697–701.

[4] Bigalke H. Properties of pharmaceutical products of botulinum neurotoxins. In: Jankovic J, Albanese A, Atassi MZ, Dolly JO, Hallett M, Mayer NH, editors. Botulinum Toxin — Therapeutic Clinical Practice & Science. Philadelphia: Saunders Elsevier; 2008. p. 389–95.

[5] Frevert J. Xeomin: an innovative new botulinum toxin type A. Eur J Neurol Dec. 2009;16(Suppl 2):11–3.

[6] Roggenkamper P, Jost WH, Bihari K, Comes G, Grafe S. Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm. J Neural Transm 2006;113(3):303–12.

[7] Benecke R, Jost WH, Kanovsky P, Ruzicka E, Comes G, Grafe S. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology 2005;64(11):1949–51.

[8] Consky E, Basinski A, Belle L, Ranawaya R, Lang AE. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS): assessment of validity and inter-rater reliability (Abstract 1199P). Neurology 1990;40(Suppl 1).

[9] Brashear A, Lew MF, Dykstra DD, Comella CL, Factor SA, Rodnitzky RL, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-responsive cervical dystonia. Neurology 1999;53(7):1439–46.

[10] Brin MF, Lew MF, Adler CH, Comella CL, Factor SA, Jankovic J, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. Neurology 1999;53(7):1431–8.

[11] Truong D, Duane DD, Jankovic J, Singer C, Seeberger LC, Comella CL, et al. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. Mov Disord 2005;20(7):783–91.

[12] Allergan, Inc.. Botox® (onabotulinumtoxinA) for injection US Prescribing Information; 2009.

[13] Truong D, Lew M, Orlova O. Efficacy of Dysport (botulinum toxin type A) for the treatment of cervical dystonia: a multicenter, randomized, double blind, placebo-controlled phase III study. Toxicon 2008;51:37.

[14] Merz Pharmaceuticals, GmbH. Data on File, Frankfurt, Germany; 2010.

[15] Comella CL, Jankovic J, Shannon KM, Tsui J, Swenson M, Leurgans S, et al. Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. Neurology 2005;65(9):1423–9.

[16] Chen F, Kuziemko GM, Amersdorfer P, Wong C, Marks JD, Stevens RC. Antibody mapping to domains of botulinum neurotoxin serotype A in the complexed and uncomplexed forms. Infect Immun May 1997;65(5):1626–30.

[17] Fujinaga Y. Interaction of botulinum toxin with the epithelial barrier. J Biomed Biotechnol 2010, doi:10.1155/2010/974943.